

Efficiency of ledipasvir/sofosbuvir treatment in hepatitis C virus infection

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Cite this article as: Bilgiç E, Çağın YF, Menteş O, Aladağ M. Efficiency of ledipasvir/sofosbuvir treatment in hepatitis C virus infection. *Intercont J Int Med.* 2025;3(3):48-52.

Received: 05.02.2025

Accepted: 02.06.2025

Published: 29.08.2025

ABSTRACT

Aims: This study analyzes the efficiency of a combination of ledipasvir/sofosbuvir (LED/SOF), a newly developed direct-acting antiviral agent, in patients infected with hepatitis C virus (HCV) with or without a treatment history [pegile-interferon±ribavirin (PEG-IFN±RBV)] who subsequently developed recurrence.

Methods: Files of hepatitis C-infected patients who received LED/SOF treatment for 3-6 months with recurrence or without a treatment history (PEG-IFN±RBV) before admission to Gülhane Training and Research Hospital between 06.06.2016 and 23.05.2018 were taken into account.

Results: This study included 45 patients, 20 of whom were female (44.4%) and 25 of whom were male (55.6%). Among those patients, 22 were administered PEG-IFN±RBV treatment and experienced recurrence, whereas 23 had no previous treatment history. Age; sex; 6-month aspartate aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin, and albumin, international normalized ratio (INR), hemoglobin (HGB) and thrombocyte (PLT) values; and 1-, 2- and 6-month-old HCV-RNA levels were evaluated in this study. When the pretreatment HCV-RNA levels and the 1st, 2nd and 6th month HCV-RNA levels were compared, the decrease in the values was statistically significant ($p<0.05$, $p<0.05$, $p<0.05$, $p<0.05$). The initial and 6-month AST, ALT, GGT, and ALB levels and the PLT were statistically significant ($p<0.05$, $p<0.05$, $p<0.05$, $p<0.05$, respectively).

Conclusion: LED/SOF treatment in patients with or without HCV infection treatment experience was found to be reliable and successful.

Keywords: RBV, PEG-IFN, HCV-RNA, LED/SOF

INTRODUCTION

Hepatitis C virus (HCV) infection is a well-known cause of chronic liver disease. The estimated number of people infected with HCV is 71 million globally.¹ Epidemiological studies performed in Türkiye have shown that its prevalence is approximately 1%.²

The purpose of HCV treatment is to achieve a sustained virologic response (SVR). The SVR defines the occurrence of aviremia in the 12th and 24th months after the commencement of treatment (SVR12-SVR24). SVR is associated with normalization of liver enzymes and suppression of necroinflammation in patients who have not yet developed cirrhosis. The possibility of relapse in patients who have achieved a SVR has decreased considerably. In patients with advanced liver deficiency (METAVIR score F3-F4), the SVR is associated with a reduction in hepatic deficiency and portal hypertension risk. In patients with advanced liver deficiency, SVR has been shown to reduce the risk of hepatocellular carcinoma (HCC) development and liver-related fatalities.³⁻⁹

Over the years, as the HCV lifecycle, genomic construction and pathogenesis have been clarified, studies on direct-acting

treatments for the virus have been conducted.¹⁰ By employing newly developed direct-acting antivirals (DAAs), regimens without interferon (IFN) and RBV have been developed. Through such treatment regimens, nearly total SVR has developed, with a definite increase in patient quality of life.¹¹ Compared with formerly used medicines, newly developed DAAs can be used reliably in patients with comorbid disorders, resulting in a greater response to treatment. Given these data, the use of DAAs has revolutionized HCV infection, demonstrating that the condition could be acceptable as a curative.^{12,13}

The purpose of our study was to analyze the efficiency of LED/SOF treatment, a directly acting antiviral agent, in HCV patients with no treatment history or recurrence.

METHODS

Selection of Cases and Compiling the Data

The files of the HCV patients who applied to Gülhane Training and Research Hospital between 06.06.2016 and 23.05.2018

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and who received LED/SOF treatment for 3-6 months, either nonexperienced or experienced to treatment later developing a recurrence, were retrospectively evaluated as per the Helsinki Declaration Resolutions, Patient Rights Regulations and ethical rules, subject to İnönü University Health Sciences Non-interventional Clinical Researches Ethics Committee (Date: 26.11.2019, Decision No:2019/414).

Age, gender, AST, ALT, ALP, GGT, total bilirubin, albumin, INR, HGB and PLT values at the beginning and 6th month of treatment, and HCV-RNA levels at the beginning and 1st, 2nd and 6th month were analyzed (HCV-RNA level and genotyping evaluated by Abbott real-time HCV assay).

HCV genotypes are classified based on phylogenetic analysis of nucleotide sequence variability, primarily within the NS5B and Core/E1 regions of the viral genome. This classification delineates HCV into seven major genotypes,¹⁻⁷ each comprising multiple subtypes (e.g., 1a, 1b, 3a), with inter-genotypic sequence divergence of approximately 30% and intra-genotypic divergence of around 15%. Genotyping is typically performed using reverse transcription polymerase chain reaction (RT-PCR) followed by sequence analysis or line probe assays. The distribution of HCV genotypes varies geographically and has significant implications for disease progression, epidemiology, and treatment response, making accurate genotypic determination a critical component of clinical management.

The treatment start and 6-month values of the patients were compared to evaluate the response to treatment. While pediatric patients were not included, those aged 18 years or older were included. Twenty-six patients were not covered because they had previously undergone a liver transplant, 10 were not covered because they failed to attend follow-up regularly, and 1 patient was not covered because of receiving RBV treatment along with LED/SOF. A total of 23 patients who did not previously receive treatment and 22 patients who underwent PEG-IFN±RBV treatment with recurrence, totaling 45 patients, were included. Among those, 44.4% were female, and 55.6% were male. The average age of the patients was 66.16 years. Our study was retrospective and did not involve any invasive procedures. İnönü University Turgut Özal Medical Center Biochemistry and Microbiology laboratory data were used.

Statistical Analysis

For the purposes of comparing the pre- and posttreatment HCV-RNA values of HCV patients at a reliability level of 95% ($\alpha=0.05$) and 80% strength ($\beta=0.20$), the minimum number of patients to be covered by the study, considering an efficiency of 0.79, was estimated to be 15. The data are presented as the average±standard deviation and number (%). Compliance with the normal distribution was carried out via the Shapiro-Wilk test. For the statistical analyses, the Friedman test, Wilcoxon test, and Spearman correlation coefficient were employed as necessary, and a p-value <0.05 was considered statistically significant.

RESULTS

A total of 45 patients, 20 women (44.4%) and 24 men (55.6%) were included in our study. Of these patients, 22 had previously received PEG-IFN±RBV treatment and relapsed; and 23 were inexperienced patients. The age of the patients

ranged between 25-90 years with a mean age of 66.16 years old. Treatment duration of the patients: 5 (22.5%) patients for 3 months and 40 (77.5%) patients for 6 months. When the patients included in study were categorized according to their genotypes: 37 (82.2%) patients were GT1b, 5 (11.1%) patients were GT1, 2 (4.4%) patients were GT4, 1 (2.2%) patient was GT1a (Figure 1).

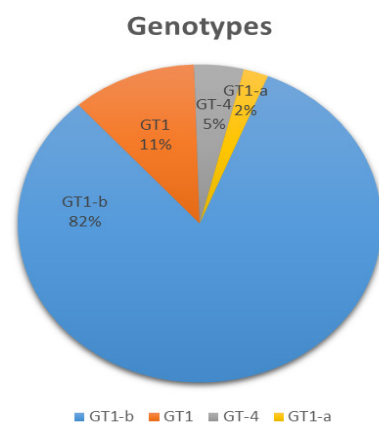


Figure 1. Genotypes of the patients

The pretreatment HCV-RNA level of the patients was 9.79 ± 17.22 million/copy, while the posttreatment 1st month HCV-RNA level was 0.12 ± 0.71 million/copy, and the 2nd and 6th month HCV-RNA levels were calculated to be 0 (zero). The decrease in the posttreatment HCV-RNA level was statistically significant ($p < 0.001$).

When the pretreatment HCV-RNA levels and the posttreatment 1st, 2nd and 6th month HCV-RNA levels were compared, the decrease in the values was statistically significant ($p < 0.05$, $p < 0.05$, $p < 0.05$ and $p < 0.05$, respectively) (Figure 2).

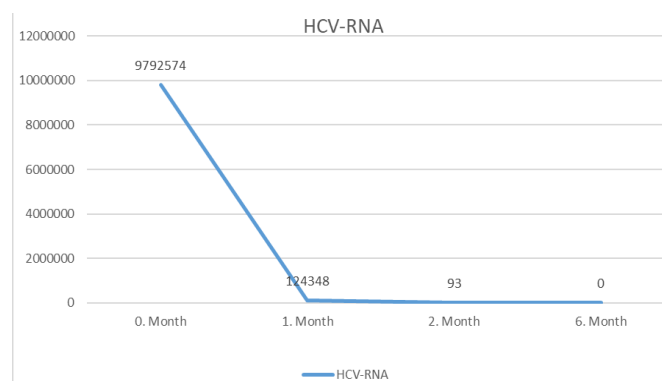


Figure 2. HCV-RNA (copy) levels according to the months of treatment
HCV: Hepatitis C virus, RNA: Ribonucleic acid

The AST, ALT, ALP, GGT, total bilirubin, albumin, INR, HGB, and PLT values were compared with the pretreatment and posttreatment 6th month values. The AST, ALT, GGT, and ALB levels and the PLT were significantly different between the starting and 6th months ($p < 0.05$, $p < 0.05$, $p < 0.05$, $p < 0.05$, $p < 0.05$, $p < 0.05$, respectively). Similarly, when the ALP, total bilirubin, INR and HGB results were evaluated separately, no statistically significant differences were detected ($p > 0.05$, $p > 0.05$, $p > 0.05$) (Table 1, 2) (laboratory values reference intervals AST: 5-34 U/L, ALT: 0-55 U/L, ALP: 40-150 U/L, GGT: 9-64 U/L, total bilirubin: 0.2-1.2 mg/dl, albumin: 3.5-5 g/dl, INR: 0.8-1.2).

Table 1. HCV-RNA, AST, ALT, ALP, and GGT values at the start and 6th months of treatment (O±SD) and p-values

Parameters	HCV-RNA (million/copy)	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)
Start (O±SD)	9.79±17.22	110.42±278.59	148.87±419.48	104.66±38.77	86.24±84.20
6 th month (O±SD)	0	26.26±10.11	23.03±15.12	87.30±31.15	31.75±17.64
p-value	<0.001	<0.001	<0.001	0.330	<0.001

O: Average, SD: Standard deviation, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase

Table 2. Total bilirubin, albumin, INR, HGB and PLT values at the start and 6th months of treatment (O±SD) and p-values

Parameters	Total bilirubin (mg/dl)	Albumin (g/dl)	INR	HGB	PLT
Start (O±SD)	1.12±0.66	3.42±0.50	1.15±0.23	13.52±2.22	158.09±73.17
6 th month (O±SD)	1.15±0.79	3.66±0.51	1.10±0.16	13.73±2.45	154.45±78.72
p-value	0.829	0.003	0.132	0.151	0.046

INR: International normalization ratio, HGB: Hemoglobin, PLT: Thrombocyte, O: Average, SD: Standard deviation

DISCUSSION

HCV infection has become one of the foremost causes of chronic liver disease.¹⁴ Over the years, as the life cycle, genomic construction and pathogenesis of HCV have clarified, treatments directly acting on the virus have been developed.¹⁰ DAAs represent a revolution in HCV infection treatment, showing that the disease could be considered curative.^{12,13} The most common HCV subtype encountered worldwide is genotype 1.¹⁵ In a previous study, the genotype frequency worldwide was as follows: GT1, 46%; GT3, 22%; GT2, 13%; and GT4, 13%.¹⁶ HCV-related studies in Türkiye revealed that, as is the case globally, the most frequently observed type was GT1b, with a frequency of 60-100%.¹⁷ In our study, GT1b (82.2%) was the most frequently observed group.

In this study, in patients with HCV infection, with or without a history of treatment (PEG-IFN±RBV), LED/SOF (NS5A/NS5B inhibitor) treatment efficiency and its impact on liver function test (LFT) values were investigated. The treatment starts and posttreatment 1st, 2nd and 6th month values were compared. In addition, the AST, ALT, ALP, GGT, total bilirubin, albumin, INR, HGB and PLT values were compared between the first and second months of treatment. Since 11 patients failed to attend their follow-up visits regularly, SVR24 was not evaluated. Since the posttreatment 1st and 2nd month HCV-RNA values of those patients were zero and treatment efficiency was monitored, the values in those months were included.

In Chen et al.¹⁸ administered LED/SOF treatment to 127 chronic HCV patients for 12 weeks with RBV (8.7%) or without RBV (91.3%). Among patients who received LED/SOF treatment without RBV, in the non-cirrhosis and cirrhosis patient groups, the SVR12 rates were 100% (39/39) and 97.3% (73/75), respectively. Compared with the pretreatment values, the reductions in the serum ALB and GGT levels were statistically significant ($p<0.001$). However, total bilirubin and the international normalized ratio (INR) were not significantly different ($p>0.05$). In our study, data supporting these findings were also obtained, and the reductions in the serum ALB and GGT levels were found to be statistically significant ($p<0.05$). The total bilirubin and INR values were not significantly different ($p>0.05$). The SVR ratio was found to be 100%.

ION studies are very important since they are first evaluations aimed at chronic HCV patients using treatment without

RBV or INF. In the ION-1 study, in GT1 patients without a treatment history, 12 weeks of LED/SOF treatment was administered and found to be effective. Adding RBV did not contribute to SVR. The failure ratio of the virological response was 0.3%.¹⁹ In our study, the SVR was 100%, which was in compliance with the literature.

In a study by Juan et al.,²⁰ 122 patients were administered LDP/SOF treatment, whereas an SVR was obtained in 112 patients. With respect to their genotypes, 98.82% (84/85) of GT1 patients, 43.75% (7/16) of GT3 patients and 100% (21/21) of GT4 patients achieved SVR. In our study, GT1 (95%) and GT4(5%) infected patients were evaluated, revealing results in compliance with the literature (SVR 100%).

In a study by Gane et al.²¹ that analyzed the efficiency of LDP/SOF treatment in GT2 patients, the SVR was 96% in patients receiving 12 weeks of treatment (25/26), whereas in patients receiving 8 weeks of treatment, the SVR was 74% (20/27). Although the difference in response rates was not statistically significant, a shorter treatment period was found to reduce the treatment response. In our study, GT1 and GT4 patients were also evaluated, with LDP/SOF treatment being applied for 12 (5/45) and 24 (40/45) weeks, resulting in an SVR of 100%.

Zeng et al.²² evaluated 187 GT1b-infected patients; in the 1st group, cirrhosis patients were administered LDP/SOF+RBV treatment for 12 weeks; in the 2nd group, non-cirrhosis patients were administered LDP/SOF+RBV for 8 weeks; and in the 3rd group, non-cirrhosis patients were given LDP/SOF treatment for 8 weeks. The SVR ratios of groups 1, 2 and 3 were 96.8% (61/63), 96.9% (63/65) and 96.9% (62/64), respectively. Among the patients in group 3, 1 patient experienced relapse at the 4th week after treatment. Overall, this study revealed that, with or without the addition of RBV, LDP/SOF treatment is efficient and reliable in GT1b patients. In our study, 82% (36/45) of the patients were infected with GT1b, whereas 29 reached SVR24, with a 100% SVR consistent with the literature.

Gane et al.,²³ in their study, administered LDP/SOF+RBV and LDP/SOF treatments to GT3 and GT6 patients. Among the GT3 patients without a treatment history, 64% (16/25) achieved SVR in the LDP/SOF treatment group, whereas 100% (26/26) achieved SVR in 26 patients subjected to LDP/SOF+RBV treatment. LDP/SOF+RBV treatment was applied to GT3 patients with a treatment history, resulting in an SVR of 82% (41/50). LDP/SOF treatment was given to GT6 patients with or without a treatment history, with an SVR of

96% (24/25). In our study, there were no GT3 or GT6 group patients, while our treatment success rates were higher. In conclusion, the treatment response of GT3 and GT6 patients was lower than that of patients with other GTs, and a better response was obtained with trio combination treatment.

Corma-Gomez et al.²⁴ compared a patient group with HIV+HCV coinfection and only with HCV infection and compared the efficiency of 8-week and 12-week LDP/SOF treatment. In 322 patients with HIV+HCV coinfection who received 8 weeks (102) and 12 weeks (220) of treatment, the SVR ratios were 92.2% and 97.3%, respectively. The relapse rates were 4.9% and 0.5%, respectively. When the patient groups subjected to 8 weeks of treatment with HCV monoinfection (51%, 107) and with HIV+HCV coinfection (49%, 102) were compared, the SVR rates were 96.3% and 92.2%, respectively. The relapse rates were 0.9% and 4.9%, respectively. In our study, patients without HIV coinfection were also evaluated, and in line with the literature, SVR rates were higher than those in HIV+HCV-coinfected patients.

In a study carried out by Akin et al.²⁵ in Türkiye, 11 liver transplant patients and 12 kidney transplant patients with HCV infection were administered LDP/SOF±RBV treatment. All kidney transplant patients and 91% of the liver transplant patients were infected with GT1. While 9 kidney transplant patients used tacrolimus as the main immunosuppressive agent, 2 used cyclosporine. All liver transplant patients used tacrolimus. Four weeks after treatment, 75% of the kidney transplant patients and 91% of the liver transplant patients achieved SVR. Twelve weeks after treatment, all patients who received either liver or kidney transplants achieved an SVR.

In this study, 45 patients infected with GT1 (95%) or GT4 (5%) were analyzed, while 24-month control data from 9 patients were inaccessible. Among those patients, the 1st or 2nd month HCV-RNA values were zero, so they were included. All patients who visited for 24-month controls²⁶ achieved SVR24. In this context, our study results are in accordance with the literature.

Limitations

The limitation of this study was the lower number of patients. In our study, patients who did not undergo liver transplantation were also evaluated, and the results were similar to those reported in the literature.

CONCLUSION

The treatment starts and posttreatment 6th month HCV-RNA levels, AST, ALT, GGT, albumin and PLT results were analyzed, and a statistically significant difference was detected in relation to the ALP, total bilirubin, INR and HGB results. These findings demonstrate that medicinal use suppressed viral replication and decreased LFT levels. With scientific developments, understanding the HCV-RNA structure and new treatments are promising. In the future, the notion of providing a cure against HCV is encouraging.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the İnönü University Health Sciences Non-interventional Clinical Researches Ethics Committee (Date: 26.11.2019, Decision No:2019/414).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Aknowledgement

This study is derived from Dr. Elif Bilgiç's Internal Medicine Specialty Thesis.

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